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THE SEARCH FOR PHENYLKETONURIA

PHENYLKETONURIA was first described 35 years ago. It is a rare disease, yet there are well over a thousand cases recorded in the literature and the number of persons screened for phenylketonuria must now be reckoned in millions. It is of some interest that the first successful screening program for phenylketonuria was conducted by Følling[1] himself at the time he discovered the disease. Having identified phenylpyruvic acid in the urine of two mentally retarded children, he then screened the urines of retarded patients in an institution for the same substance and found it in several of them. This was the standard method of case-finding for more than 20 years. During this time it was established that phenylketonuria was an inborn error of phenylalanine metabolism, that it was inherited as an autosomal recessive and that it accounted for about 1% of the institutionalized, Caucasian, mentally retarded population.

Phenylketonuria remained not much more than an academic curiosity until it was shown that the biomedical abnormalities could be controlled by a low phenylalanine diet. This aroused clinical interest, and case-finding became concentrated on the younger sibs of known patients in the hope that dietary treatment, given early, would prevent the severe mental retardation which seemed to be a constant feature of the disease. The results were encouraging. This method of case-finding, however, meant that in each family at least one affected child would go untreated until symptoms appeared.

It seemed natural to extend the search for phenylketonuria to the infant population at large, and in the late 1950's and early 1960's several large-scale programs for screening young babies were launched in Britain,[2] the United States,[3] Canada[4] and elsewhere, using urine tests. Early asymptomatic cases were discovered in the first months of life, but experience soon showed that urinary screening tests were far from reliable at this age. Some of the least reliable results were reported from Britain, where it was found that "the Phenistix screening test for phenylketonuria in newborn infants, when used routinely at the recommended age of 4 to 6 weeks, passes as normal a substantial proportion—perhaps between a quarter and a half—of children with the disease, who are then diagnosed only after brain damage has occurred."[5] The missed cases were probably due more to the failure of young phenylketonurics to excrete phenylpyruvic acid than to the failure of the screening tests themselves. Repeated tests, at intervals up to the age of 6 months, were advised, but in most programs it proved difficult to ensure that all the babies in a community were adequately screened.

In 1961 Robert Guthrie devised a simple method of measuring phenylalanine, based on a bacterial inhibition assay. This test required only the small amounts of blood obtainable from a heel prick, and it could be used as a screening test for phenylketonuria in the first days of life. An added advantage, in North America at least, was that at this age most of the newborn population was "captive" in hospital, so there was less need to rely on the co-operation of parents, public health nurses, family doctors and pediatricians to achieve 100% coverage. A massive newborn screening program was soon started in the United States, using the Guthrie test, and it continues to date; in some states the test is now required by law. Other screening tests such as chromatography or fluorimetry in which blood is used have since been described, but they have been used less widely. A number of screening programs for phenylketonuria in the newborn are now in progress in other countries,[6-8] and in Britain the Health Service is about to change from urinary to blood screening tests.

This issue of the Journal carries an account of a newborn screening program for phenylketonuria in Ontario (page 185). The program is voluntary but organized and supported by the Maternal and Child Health Service of the Ontario Department of Health with the help of a PKU Advisory Committee. The Committee's report describes the results obtained in the first 2½ years. Although over 96% of the newborn population was screened in the first full year, this fell to 86.5% in the second year. The reasons seemed to be random rather than systematic, and it looks as though there will be continued difficulties in reaching and maintaining 100% coverage for some time to come. The screening test used was the Guthrie test. No mention is made of false negatives, such as reported from Britain with Phenistix, but there is still time for these to turn up; false negative Guthrie tests have been observed in other programs.[9] There were about 10 false positive tests for each true positive test; premature attempts to lower this

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ratio by reducing the sensitivity of the screening test may be ill-advised since it seems that in most screening procedures the proportion of false positives is inversely related to the proportion of false negatives, so that the one cannot be lowered without raising the other.[10]

From the 272,108 screening tests carried out in the 2½ years, 19 cases of phenylketonuria were found; this is an incidence of approximately 1 in 14,300 live births. Of these 19 cases, however, 14 were regarded as "classical" and five as "atypical" phenylketonuria. This gives an incidence of about 1 in 19,400 live births for "classical" phenylketonuria and about 1 in 54,000 for the "atypical" form. These figures correspond very closely with those of Berman *et al.*[9] derived from a similar type of screening program in the United States, although there are differences between the series in the definition of "atypical" cases.

"Atypical" phenylketonuria is still something of a mystery; there may well be several causes of persistently raised blood phenylalanine levels. In part "atypical" phenylketonuria is an artefact of blood screening, since many of the cases have negative urinary screening tests. Furthermore, many cases seem symptomless and some may lose their hyperphenylalaninemia with increasing age. The study of this condition may throw light on the pathogenesis of "classical" phenylketonuria; it seems clear already that a raised blood phenylalanine level *per se* (at least up to 20 mg. per 100 ml.) is not necessarily harmful. In practice, "classical" and "atypical" forms of phenylketonuria are hard to distinguish in the neonatal period and both tend to be given dietary treatment; as the Committee stresses, this may be particularly dangerous in the "atypical" form. The comparatively recent recognition of "atypical" phenylketonuria has complicated the assessment of low phenylalanine diets. In addition, it is now known that not all cases of untreated "classical" phenylketonuria are severely mentally retarded. These facts have led to some pointed criticism both of widespread screening, especially those programs required by law,[11] and of the dietary treatment of phenylketonuria.[12] The Committee has not entered this controversy but accepts that the early dietary treatment of phenylketonuria is beneficial. Most evidence for the good effects of dietary treatment seem to outweigh the arguments against it.[9] Nevertheless it is still important to collect data on this point as well as on how strict the diet needs to be, how long it should be continued, and its place in the management of the pregnant woman with phenylketonuria.

Screening programs are becoming increasingly popular. Formerly, screening for disease was used to exclude diseased persons from the Armed Services or insurance schemes, to prevent the spread of infection, or to collect information for epidemiological or genetic surveys. Many of today's programs aim to detect diseases such as phenylketonuria, diabetes mellitus, glaucoma or carcinoma of the cervix before symptoms appear, on the plausible assumption that treatment then will give better results than treatment at the symptomatic stage when the patient would ordinarily come under medical care. Screening tests are offered to, or even forced upon, persons who regard themselves as healthy and have not sought medical advice. The approach of the screener often differs from the traditional approach of the physician, who does the best he can for the patient who consults him. As Cochrane[13] points out, "the screener's approach is technically 'evangelical'. He proclaims his ability to help, and because he is a doctor many people believe him and submit to screening. He must therefore be very careful that his claims . . . can be substantiated." As a recent authoritative study of several screening programs emphasizes,[14] this may be very hard for the screener to do. Screening tests for a wide range of metabolic disorders are now technically feasible. It does not follow, however, that just because the means to screen for a disease are available this should be done. Screening programs are costly in time, money and medical facilities as well as in anxiety to those with false positive tests and in wrongful reassurance to those with false negative tests. Where medical resources are limited, it should be quite clear before a community-wide program is embarked upon that the benefits of screening for a particular disease warrant the cost. It is to be hoped that the vast experience in searching for phenylketonuria which is now accumulating in so many countries will be used wisely in the design of future large-scale screening programs for this and other diseases.

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PROTECTION OF HUMAN RIGHTS IN MEDICAL RESEARCH

THE National Institutes of Health in the United States and some of the granting agencies in Canada now require the recipients of grants for research in which the testing of human subjects is involved to give assurance that the proposed projects have been considered by a committee specially appointed to safeguard the rights of the subjects.

The Declarations of Helsinki and Geneva and the Nuremberg Code set forth principles intended to ensure that the known risks of the project do not outweigh its potential benefits and that the consents given by subjects participating in the project are voluntary and based on adequate information. A physician should remind himself repeatedly that he may not subject a patient to any procedure unless he believes it is in the patient's interest and unless the patient has given his informed consent. This restriction applies to the withdrawal of one extra millilitre of blood, one extra puncture by a needle, administration of one extra dose of drug or even placebo, or the taking of one extra radiograph.

It has been suggested that a physician engaged in research may consider a procedure as therapeutic or diagnostic if he can honestly state that he would carry it out even if no element of research were involved. A doctor's sincere belief that a procedure will do no harm does not permit him to take liberties with the body or mind of the person who has come to him for help. The possibility that the procedure may result in some benefit to society or even provide further knowledge about the patient's disease does not excuse an assault or battery; it must be shown that the knowledge to be gained can be expected to benefit the patient concerned.

When it has been decided that the procedure is not therapeutic or diagnostic or mainly in the interests of the patient, an informed consent must be obtained. Is verbal consent sufficient or must consent always be in writing? Investigators frequently complain that volunteers will be frightened away if a written consent is required because people become suspicious when they are asked to sign a document. Laymen, on the other hand, tend to be of the opinion that a written document tells them what is actually going to happen; a verbal explanation may be less informative. Everyone would agree that if the need should arise, it is far easier to prove what the explanation was if it is in writing. Where the risk and the discomfort are both truly minimal, a belief which must be in the mind of the patient as well as of the investigator, a written consent may be of less importance, provided there is some accurate record of the explanation and consent. To proceed without written consent, however, where there is any real possibility of risk or discomfort, is inviting trouble.

The consent forms should be suited to the individual project, and the amount of detail they include will vary with the subject's intelligence, experience and knowledge. It should be phrased in terms as simple as possible, and technical jargon should be avoided. It should clearly state the general nature of the proposed procedures as well as their known risks and discomforts; that the project is a research undertaking and not expected to benefit the subject; that (if this be the case) there may be unknown reactions; and that the patient consents to be a subject on the understanding that he may withdraw from the project at any time. Investigators who have used a written consent of this kind have found that the number of subjects who have refused to take part in projects is not sufficiently large to prevent the projects from being completed.

Who may give his consent? In the words of the Declaration of Helsinki: "The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise fully his power of choice." This statement implies that the subject must be free to accept or refuse any request to participate in a research project. There is wide variation in the extent to which prisoners, members of the armed forces, institutionalized persons, students and employees enjoy true freedom of choice in certain circumstances. Such persons constitute a "captive" group and the principles applicable to them have not yet been clearly determined. In situations of this kind it is wise to err on the side of conservatism.